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Synthesis And Spectral Studies Of 7-Chloro-2, 3-Dihydro-1, 4-Benzothiazine And Its 4-(N-Phenylamido) And 4-(N-Nitroso-N-Phenylamido) Derivatives

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Abstract

Heterocyclic compounds are widely used to synthesize a wide range of drugs with various pharmacological activities. They have been shown significant role in the field of biochemistry, medicinal chemistry, agricultural chemistry etc. Most of the enzymes, hormones, vitamins, nucleic acids (RNA and DNA), alkaloids, pigments and antibiotics contain heterocyclic compounds. Phenothiazine which is a tricyclic compound having thiazine nucleus possesses outstanding therapeutic value in human and veterinary medicine by virtue of their activity upon the parasympathetic nervous system. These also have significant antitumor activity. Their antitumor activity has been assigned to their interaction with DNA via complexation. Due to structural similarities with phenothiazines 1, 4-benzothiazines also show a wide spectrum of biological activities and have widespread use in therapeutic medicines. In the present work 7-chloro-2, 3-dihydro-1, 4-benzothiazine nucleus heterocyclic nitrogen has a side chain at 4- position which constitutes a nitrosourea linkage and as such these compounds contain both 1, 4-benzothiazine nucleus and nitrosourea linkage. Antitumor activities of some of the derivatives of these compounds have also been reported.[5-6]

Key words

Phenothiazines, 1, 4-Benzothiazines, 4-(N-nitroso-N-phenylamido) derivatives, Nitrosoureas, Antitumor activity, Alkylation, Complexation

Introduction

Nitrosoureas are cytotoxic chemotherapeutic agents as they demage DNA and are used to treat various malignancies including brain tumors, lymphomas and pancreas cancer. Lipophilic character of the nitrosoureas is an important property due to which they have the ability to cross the blood-brain barrier whereas many antitumor agents failed to do so. Some common nitrosoureas are carmustine (BCNU), streptozotocin, lomustine (CCNU), fotemustine, 2-chloroethyl nitrosourea (CNU), 1, 3-bis (cyclohexyl)-1-nitrosourea (BCyNU), 1-methyl-3-nitro-1-nitrosoguanidine (MNNG) etc. They are alkylating agents that

interfere with DNA replication and ultimately causing DNA damage. Nitrosoureas may also be used in combination with other chemotherapeutic agents or radiation therapy. Their clinical use is limited however because of their toxicity and side effects. The most common side effect is delayed and dose – dependent myelosuppression. Thus it is worthwhile to synthesize new nitrosoureas with minimum toxicity and side effects. As currently synthesized compound contains both 2 3-dihydro-1 4-bezothiazine nucleus and nitrosourea linkage, will interact with DNA by complexation as well as alkylation and will act as bifunctional anticancer agent.

Synthesis method

5-Chloro-2-(2-aminophenylthio) ethanol (compound 3, fig. 1) synthesized by the reaction of 2-amino-5-chlorobenzenethiol (compound 1, fig.1) with ethylene chlorohydrin.

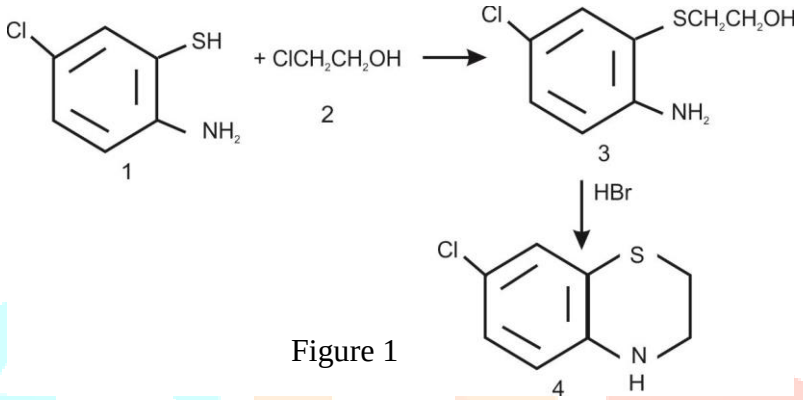
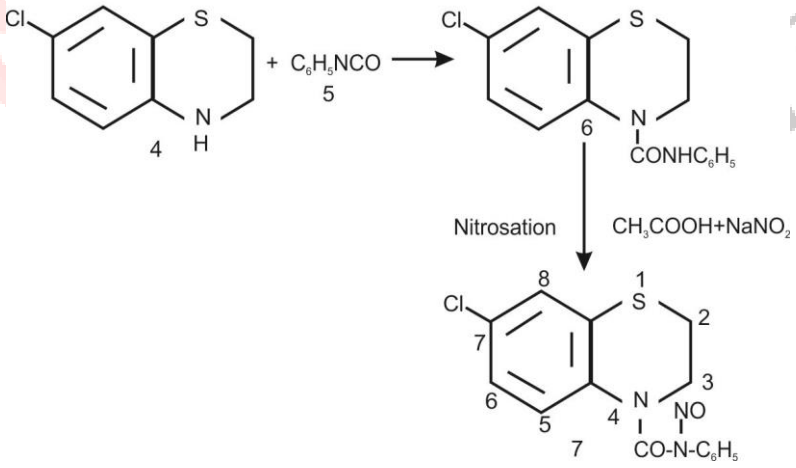


Figure 1

Dehydration of 5-chloro-2-(2-aminophenylthio) ethanol with hydrobromic acid resulted 7-chloro-2, 3-dihydro -1, 4-benzothiazine (compound 4, fig. 1). 7-Chloro-2, 3-dihydro-1, 4-benzothiazine converted into 7-chloro-4-(N-phenylamido) -2, 3-dihydro-1, 4-benzothiazine (compound 6, fig.2) by the reaction with phenyl isocyanate. Compound 6 on nitrosation with acetic acid and sodium nitrite converted into 7-chloro-4-(N-nitroso-N-phenylamido)-2,3-dihydo-1,4-benzothiazine (compound 7, figure 2).



Physical data of the synthesized compounds

Compound 3. **5-Chloro-2-(2-aminophenylthio) ethanol**

IR: 3400-3160 cm^{-1} (NH_2 stretching vibrations band overlapped by broad OH stretching vibrations band), 735 cm-1 (C-Cl-stretching)

^{1}H NMR ($CDCl_3$):

δ 7.96-6.99 ppm (multiplet due to 3H aromatic protons), δ 4.55 ppm (singlet due to 3H, NH_2 peak overlapped by OH peak), δ 3.88-3.69 ppm (triplet due to CH_2 protons attached to oxygen), δ 3.44-3.25ppm (triplet due to CH_2 protons attached to sulphur). Anal. data for $C_8H_{10}NSOCl$: Calcd. C 47.17, H 4.94; Found C 47.38, H 4.91

Compound 4. **7- Chloro-2, 3-dihydro-1, 4-benzothiazine**

IR: 3300 cm^{-1} (N-H-stretching), 760 cm-1 (C-Cl-stretching)

^{1}H NMR ($CDCl_3$):

δ 7.42-6.65 ppm (multiplet due to 3H aromatic protons), δ 4.19 ppm (singlet due to NH proton), δ 4.02-3.77 ppm (triplet due to CH_2 protons at C_3), δ 3.40-3.23 ppm (triplet due to CH_2 protons at C_2). Anal. data for C_8H_8NSCl: Calcd. C 51.75, H 4.34, N 7.54; Found C 51.59, H 4.36, N 7.58

Compound 6. **7-Chloro-4-(N-phenylamido)-2, 3-dihydro-1, 4-benzothiazine**

IR: 3270 cm^{-1} (N-H-stretching), 1660 cm^{-1} (co stretching), 755 cm-1 (C- Cl -stretching),

^{1}H NMR ($CDCl_3$):

δ 7.32-6.43 ppm (multiplet due to 8H aromatic protons), δ 6.37 ppm (singlet due to NH proton), δ 3.77-3.36 ppm (triplet due to CH_2 protons at C_3), δ 3.05-2.75 ppm (triplet due to CH_2 protons at C_2). Anal. data for $C_{15}H_{13}N_2SOCl$: Calcd. C 59.11, H 4.30; N 9.19 Found C 59.46, H 4.28 N 9.24

Compound 7. **7-Chloro-4-(N-nitroso-N-phenylamido)-2, 3-dihydro-1, 4-bemzothiazine**

IR: 1600cm^{-1} (co stretching), 715 cm-1 (C- Cl -stretching),

^{1}H NMR ($CDCl_3$):

δ 7.39-6.44 ppm (multiplet due to 8H aromatic protons), δ 3.72-3.37 ppm (triplet due to CH_2 protons at C_3), δ 2.99-2.78 ppm (triplet due to CH_2 protons at C_2). . Anal. data for $C_{15}H_{12}N_3SO_2Cl$: Calcd. C 53.97, H 3.62, N 12.59 Found C 53.55, H 3.60 N 12.55

The purity of the synthesized compounds was checked by thin layer chromatography (TLC). The infrared spectra were recorded at a Perkin-Elmer spectrophotometer model 577. The ^{1}H NMR spectra were recorded at a 90 MHz Jeol FX 90 Q NMR in $CDCl_3$ containing TMS as internal standard.

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